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Dietary Nitrosamines, Heterocyclic Amines, and Risk of Gastric Cancer: A Case-Control Study in Uruguay

Eduardo De Stefani, Paolo Boffetta, Maria Mendilaharsu, Julio Carzoglio, and Hugo Deneo-Pellegrini

Abstract: *To study the effects of dietary chemicals like nitrosodimethylamine and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine, resulting from the cooking method of red meat, on gastric carcinogenesis, a case-control study was conducted in Uruguay, a country with areas of high rates of gastric cancer. The study involved 340 cases and 698 controls, who were interviewed between January 1993 and December 1996. Dietary nitrosodimethylamine was associated with an increased risk of gastric cancer [odds ratio (OR) = 3.6, 95% confidence interval (CI) = 2.4–5.5], whereas dietary 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (a potent mutagen derived from the frying and broiling of red meat) showed an OR of 3.9 (95% CI = 2.3–6.4). Both chemicals displayed independent effects, and its interaction followed a multiplicative model with an elevated OR of 12.7 (95% CI = 7.7–21.2). These results suggest that salted and barbecued meat, frequent items in the Uruguayan diet, and the resulting chemicals from the cooking methods of both types of meat are significantly associated with a high risk of stomach cancer.*

Introduction

Despite the marked decline in its mortality (1), gastric cancer remains as one of the major public health problems in Uruguay, with age-adjusted incidence rates of 20.4 and 9.3 per 100,000 in men and women, respectively (2). In particular, high incidence rates were detected in the northeastern counties of Uruguay (34.8 for men and 29.9 for women) (2). According to previous surveys (3), 50% of the population in these high-risk areas frequently consumes salted meat. In a similar way, 80% of this population consumes a large amount of barbecued meat. A previous case-control study in the Uruguayan population revealed a 60% increased risk of gastric cancer associated with salted meat intake (4). Previous studies on the association between salted fish and gastric cancer revealed an increased risk for this neoplasm (5–10). Recently, a new mutagen (2-chloro-4-methylthiobutanoic acid) has been identified in salted fish (11–13). Salted fish also contains a variety of chemicals, including volatile *N*-nitrosamines, that have proved to be carcinogenic in humans (10). The method of preparation is similar for salted meat and salted fish; thus presumably salted meat is a rich source of volatile nitrosamines and 2-chloro-4-methylthiobutanoic acid. Also, barbecued and fried red meat is a source of heterocyclic amines, a group of potent mutagens and carcinogenes (14). Therefore, this study was designed to estimate the risk of gastric cancer for dietary nitrosamines and for heterocyclic amines resulting from frying and broiling red meat.

Materials and Methods

Selection of Cases

In the period 1993–1996, all newly diagnosed and microscopically confirmed patients with gastric cancer admitted to the four major hospitals in Montevideo, Uruguay were considered eligible for this study. In total, 361 cases of gastric cancer were identified. From this initial series, 10 patients refused the interview and 11 were too ill to be interviewed, leading to a final total of 340 patients with gastric cancer (response rate 94.2%). Two-hundred seventy patients (79.4%) presented tumors in the antrum and pylorus, 20 were afflicted with cancer of the cardia, 20 presented diffuse tumors compromising the whole stomach, and 30 were afflicted with cancer of the corpus. When the tumors were classified according to the Lauren classification, 230 (67.6%) were of the intestinal type and 36 (10.6%) were of the diffuse type; the remaining 74 patients (21.8%) presented tumors that could not be classified by the Lauren scheme.

Selection of Controls

All controls were selected from the same hospitals and in the same period as the cases. Conditions for eligibility

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were as follows: 1) 25–84 years of age, 2) free of conditions related to the digestive tract or nutritional disorders, and 3) free of conditions related to tobacco and alcohol consumption. A total of 698 patients were selected as controls, with a response rate of 91.5%. The most frequent conditions among controls were eye disorders (209 patients, 29.9%), abdominal hernia (128 patients, 18.3%), skin diseases (64 patients, 9.2%), osteoarticular diseases (51 patients, 7.3%), and fractures (47 patients, 6.7%) (Table 1).

Interviews

Cases and controls were interviewed shortly after admission to the hospital (mean time after admission 26 days) by two trained social workers. The questionnaire included the following sections: 1) sociodemographic variables, 2) a complete tobacco history, 3) a complete alcohol consumption history, and 4) a food-frequency questionnaire, including the following items: beef, lamb, salted meat, barbecued meat, salami, saucisson (a type of salami frequently consumed in France), mortadella (a type of ham of Italian origin), ham, cheese, milk, butter, oil for dressing salads, carrot, tomato, lettuce, onion, spinach, potato, sweet potato, orange, apple, pear, grape, peach, banana, beer, wine, hard liquor, and "mate." Although it is acknowledged that this food-frequency questionnaire is rather limited, precluding the calculation of total energy intake, it nevertheless is detailed concerning meat items, which are the main objective of this study. It also allowed calculation of several approximated indexes of micronutrients and related chemicals: methionine, nitrite, nitrosodimethylamine (NDMA), 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), vitamin C, and β-carotene. The intake of micronutrients (methionine, vitamin C, β-carotene) and related chemicals (NDMA and heterocyclic amines such as PhIP) was computed by multiplying the frequency of each unit of food by the nutrient content of a standard average portion for a patient 50–69 years of age. Micronutrient values were derived from local food tables (15), whereas values for NDMA and PhIP were obtained from sources from other populations (16–28). Because the questionnaire assessed the proportion of different meats cooked by frying, broiling, or salting, intake of PhIP and NDMA was calculated as follows: frequency of consumption of fried, broiled, or salted meat × [(portion size (g) × PhIP or NDMA content for each fried or salted meat according to literature data)/100 g].

Table 1. Distribution of Controls by Disease Category

ICD-9	Category	No.	%
360–379	Eye disorders	209	29.9
550–553	Abdominal hernia	128	18.3
680–709	Skin diseases	64	9.2
710–739	Osteoarticular diseases	51	7.3
800–959	Fractures and trauma	47	6.7
280–289	Blood disorders	40	5.7
1–136	Infectious diseases	39	5.6
540	Acute appendicitis	34	4.9
380–389	Ear disorders	32	4.6
580–629	Genitourinary diseases	28	4.1
454	Varicose veins	26	3.7
Total		698	100.0

Statistical Analysis

Relative risks of stomach cancer, approximated by the odds ratios (ORs), were estimated for all food groups and food items, as well as for micronutrient and related chemicals. The method used was unconditional logistic regression (29), and all the models included the matching variables (age, sex, and residence) as well as all the relevant confounders (urban/rural status, duration of tobacco use, total alcohol consumption, and "mate" drinking). Effect modification was tested by the introduction of interaction terms in all models, whereas the trend test for each variable was calculated after the unfactorized variable was entered as a continuous term to a model with all the potential confounders. The ORs for all dietary variables were also estimated after the variables were entered as continuous terms, one by one, in a model containing the major confounders and the matching variables. Finally, all dietary variables were introduced simultaneously as continuous terms in a model in which major confounders were represented, following the model suggested by Howe and Burch (30). Although the model includes highly correlated nutrients or foods, computer simulation has shown that the estimates are statistically stable. Quoting Howe and Burch, in these models, those nutrients that contribute to energy contain the energy and nonenergy effects of that nutrient. All calculations were performed with the GLIM software (31).

Results

The distribution of cases and controls by sociodemographic variables is shown in Table 2. Because both series (cases and controls) were frequency matched on age, sex, and residence, the percent distribution on these variables was very similar. Cases showed a slightly higher proportion of rural residents than controls, whereas cases displayed lower monthly incomes than controls.

ORs of stomach cancer for men, women, and both sexes combined for food items and micronutrients are shown in Table 3. The food variables were entered as continuous terms in a model that included the matching variables (age, sex, and residence) plus major confounders (urban/rural status, duration of tobacco use, total alcohol consumption, and "mate" drinking). Thus ORs should be interpreted as resulting from the change per unit of the variable. Among both sexes combined, the highest OR was observed for barbecued meat [OR = 2.0, 95% confidence interval (CI) = 1.7–2.5]. Salted meat was associated with an increased risk of 1.7 (95% CI = 1.4–2.1). Among micronutrients, methionine (OR = 1.6, 95% CI = 1.3–1.9), NDMA (OR = 1.5, 95% CI =

Table 2. Distribution of Cases and Controls by Sociodemographic Characteristics[a]

	Cases	Controls
Age, yr		
25–29	3 (0.9)	7 (1.0)
30–39	17 (5.0)	39 (5.6)
40–49	16 (4.7)	32 (4.6)
50–59	60 (17.6)	120 (17.2)
60–69	101 (29.7)	211 (30.2)
70–79	114 (33.5)	230 (33.0)
80–84	29 (8.5)	59 (8.5)
Sex		
Male	224 (65.9)	459 (65.8)
Female	116 (34.1)	239 (34.2)
Residence		
Montevideo	134 (39.4)	283 (40.5)
Other counties	206 (60.6)	415 (59.5)
Urban/rural status		
Urban	219 (64.4)	477 (68.3)
Rural	121 (35.6)	221 (31.7)
Education, yr		
0–5	55 (16.2)	214 (30.7)
≥6	285 (83.8)	484 (69.3)
Income, US $/yr		
≤125	121 (35.6)	225 (32.2)
126–152	129 (37.9)	225 (32.2)
≥153	90 (26.5)	248 (35.5)
No. of patients	340 (100)	698 (100)

a: Values in parentheses are percentages.

1.3–1.7), and PhIP (OR = 1.9, 95% CI = 1.6–2.2) were associated with a significantly elevated risk of gastric cancer. Vegetables, fruits, vitamin C, and β-carotene were associated with significantly reduced risks.

ORs of stomach cancer for NDMA and PhIP indexes are shown in Table 4. Dietary NDMA intake was associated with an increased risk of gastric cancer, with an OR of 3.6 (95% CI = 2.4–5.5) for the highest category of exposure. The dose-response pattern was highly significant. Similarly, exposure to PhIP from dietary sources displayed a significant dose-response pattern, with an OR of 3.9 (95% CI = 2.3–6.4) for the highest level of exposure. The interaction between both chemicals showed a multiplicative pattern with a rather high OR of 12.7 (95% CI = 7.7–21.2) for high levels of exposure of both chemicals.

ORs of gastric cancer for all foods and nutrients adjusted simultaneously for each other are shown in Table 5. Concerning food items, the highest OR was observed for barbecued meat (OR = 2.2, 95% CI = 1.8–2.6), followed by salted meat (OR = 1.5, 95% CI = 1.2–1.9). When nutrients and related chemicals like NDMA and PhIP were entered simultaneously in the same model, NDMA and PhIP were associated with significantly elevated ORs. Methionine and β-carotene were no longer significant, and β-carotene even changed the direction of its association with gastric cancer risk.

Discussion

This study showed increased risks of gastric cancer associated with barbecued meat, salted meat, and NDMA and PhIP indexes. Joint exposure to NDMA and PhIP showed a high risk of stomach cancer, and when all variables were entered simultaneously in the same model according to the suggestion of Howe and Burch (30), NDMA and PhIP remained as significantly elevated variables. Therefore, dietary exposures to nitrosamines and heterocyclic amines appear to be important risk factors for gastric cancer in the Uruguayan population.

Previous studies on nitrosamine intake (or surrogate measures for these chemicals) were consistent in showing an elevated risk of stomach cancer (4,32). Therefore, exogenous *N*-nitroso compounds are likely to be as important as endogenous nitrosation in increasing the risk of stomach cancer (32).

Table 3. ORs of Gastric Cancer Associated With Food Items, Micronutrients, and Related Substances[a,b]

	Men		Women		Both	
	OR	95% CI	OR	95% CI	OR	95% CI
Red meat	1.39	1.06–1.80	1.44	1.02–2.03	1.40	1.15–1.70
Barbecue	2.38	1.82–3.11	1.47	1.09–1.98	2.02	1.66–2.47
Salted meat	1.59	1.26–2.02	2.00	1.36–2.95	1.71	1.39–2.08
Processed meat	1.15	0.91–1.45	0.96	0.72–1.28	1.04	0.86–1.25
Vegetables	0.39	0.31–0.50	0.51	0.38–0.70	0.43	0.36–0.52
Fruits	0.42	0.34–0.53	0.43	0.31–0.59	0.43	0.35–0.51
Methionine	1.58	1.23–2.04	1.69	1.22–2.36	1.62	1.32–1.98
Nitrites	0.52	0.43–0.62	0.79	0.62–1.01	0.55	0.48–0.62
NDMA	1.63	1.39–1.91	1.34	1.08–1.67	1.51	1.33–1.72
PhIP	1.88	1.58–2.23	1.48	1.15–1.91	1.87	1.63–2.16
Vitamin C	0.35	0.28–0.43	0.43	0.35–0.56	0.39	0.33–0.45
β-Carotene	0.47	0.39–0.56	0.58	0.47–0.72	0.51	0.44–0.58

a: Each variable is adjusted for age, sex (for estimates concerning both sexes combined), residence, urban/rural status, smoking duration, alcohol consumption, and "mate" consumption.

b: Abbreviations are as follows: OR, odds ratio; CI, confidence interval; NDMA, nitrosodimethylamine; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine.

Table 4. ORs of Gastric Cancer for NDMA and PhIP Dietary Exposures[a]

Interquartile Range	No. Cases	No. Controls	OR	95% CI
		NDMA[b]		
≤0.14	45	215	1.0	
0.15–0.18	79	180	2.07	1.36–3.18
0.19–0.26	105	154	3.23	2.13–4.89
≥0.27	111	149	3.62	2.38–5.51
		PhIP[b]		
≤8.5	34	226	1.0	
8.6–13.9	70	189	2.07	1.36–3.18
14.0–17.7	110	151	3.10	1.92–5.01
≥17.8	126	132	3.86	2.34–6.37

NDMA	PhIP	Cases	Controls	OR	95% CI
		NDMA-PhIP interaction			
Low	Low	27	206	1.0	
High	Low	77	209	3.07	1.87–5.03
Low	High	97	189	4.36	2.68–7.08
High	High	139	94	12.73	7.67–21.15

a: ORs were adjusted for age, sex, residence, urban/rural status, tobacco duration, total alcohol consumption, and "mate" drinking.
b: For NDMA, χ^2 for trend = 40.22, $p < 0.001$; for PhIP, χ^2 for trend = 83.04, $p < 0.001$.

Recently, heterocyclic amines (or surrogates of them) have been suggested as important risk factors for colon, breast, and stomach cancers (33–40). The Uruguayan population is characterized by a very high consumption of red meat, which is usually prepared by frying or broiling, and thus this food item is a rich source of heterocyclic amines (41). Concerning the mechanisms by which exogenous nitrosamines and heterocyclic amines could act in gastric carcinogenesis, direct contact of these mutagens with the gastric mucosa is likely. More specifically, heterocyclic amines are potent genotoxic agents (41).

Table 5. ORs for Food Items and Micronutrients, Included Jointly in a Single Model as Continuous Terms[a]

	OR	95% CI
	Food items	
Red meat	1.34	1.06–1.68
Barbecued meat	2.16	1.76–2.64
Salted meat	1.49	1.19–1.86
Processed meat	0.96	0.79–1.17
Vegetables	0.49	0.40–0.60
Fruits	0.55	0.45–0.69
	Micronutrients	
Methionine	1.19	0.90–1.57
Nitrite	0.53	0.42–0.67
NDMA	1.58	1.25–2.00
PhIP	1.54	1.24–1.91
Vitamin C	0.63	0.43–0.91
β-Carotene	1.31	0.97–1.76

a: ORs were adjusted for each other and for age, sex, residence, urban/rural status, tobacco duration, total alcohol consumption, and "mate" drinking.

Experimental studies have reported that heterocyclic amines, including PhIP, and nitrosamines, including NDMA, are carcinogenic to rodents, inducing cancers of the liver, kidney, colon, and mammary glands (10,42). However, these compounds were not demonstrated to induce cancer in the glandular stomach (10,34). These findings could be explained as due to species differences between rodents and humans.

Like other case-control studies using hospitalized controls, this study has limitations and strengths. The possibility that hospital-based controls presented dietary changes is difficult to rule out. An important limitation of this study is related to the short food-frequency questionnaire, which precluded the calculation of total energy intake. This could result in misclassification of the exposure, although this presumably affected cases and controls similarly, leading the results to the null. Among the strengths, the statistical power, the almost complete participation rate of cases and controls, the absence of proxy responses, and the similar catchment areas are against selection bias. Because the food-frequency questionnaire employed in this study is short, the estimation of total energy intake was not possible. Furthermore, although the questionnaire was not validated, it was tested for reproducibility with consistent results.

In summary, this case-control study suggests that red meat intake and chemicals resulting from its cooking are associated with a significant increase in the risk of gastric cancer in the Uruguayan population.

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This study was supported by a grant from the Comisión Honoraria de Lucha contra el Cáncer, Montevideo, Uruguay. Address reprint requests to Dr. Eduardo De Stefani, Registro Nacional de Cáncer, Avda Brasil 3080 dep 402, Montevideo, Uruguay. Phone: 598 2 708 23 14. FAX: 598 2 402 08 10.

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